

Public Policy and Pharmaceutical Innovation

by Henry G. Grabowski

Historically, new drug introductions have played a central role in medical progress and the availability of cost-effective therapies. Nevertheless, public policy toward pharmaceuticals has been characterized in recent times by increasingly stringent regulatory controls, shorter effective patent terms, and increased encouragement of generic product usage. This has had an adverse effect on the incentives and capabilities of firms to undertake new drug research and development activity. The industry has experienced sharply rising research and development costs, declining annual new drug introductions, and fewer independent sources of drug development. This paper considers the effects of government regulatory policies on the pharmaceutical innovation process from several related perspectives. It also examines the merits of current public policy proposals designed to stimulate drug innovation including patent restoration and various regulatory reform measures.

Editor's Note: The Department of Health and Human Services is reviewing methods to improve the drug approval process. Proposed regulations are planned for issuance in the fall, 1982. The issues included in this article will not necessarily be reflected in the proposed regulatory changes.

Introduction

Industrial innovation in the pharmaceutical industry is currently subject to a number of conflicting forces and trends as we enter the final decades of the twentieth century.

In terms of scientific knowledge and capabilities, there is a growing excitement about the possibilities for the development of significant new therapies. The Federal government has supported health research and development well in excess of one billion dollars annually since the mid-sixties. Several important discoveries have occurred in basic biomedical research. These provide the foundation for the design of pharmaceuticals that offer much more effective remedies in several major disease areas.

Major research programs are currently being undertaken in several therapeutic areas including anti-virals, cardiovascular, neurological diseases, and can-

This paper draws on a number of my research projects performed at Duke University over the past five years which were supported by the National Science Foundation and the Duke University Center for the Study of Business Regulation. A monograph-length study on this subject, co-authored with my colleague John Vernon, is currently in press and will be published later in 1982. The views expressed herein are my own rather than those of any other individual or sponsoring institution.

cer. As Dr. Pedro Cuatrecasas (1980), former medical research scientist at Johns Hopkins University and now head of research and development (R and D) at Burroughs Wellcome has observed, "The scientific opportunities couldn't be better and the complementarity of talents and resources in the academic and industrial sectors is excellent and exciting." His optimism concerning the scientific prospects for major drug advances is echoed by research directors at several of the leading pharmaceutical firms (Bylinsky, 1976; Magnet, 1981).

Somewhat paradoxically, however, the basic thrust of most U.S. public policy in recent years has been to constrain rather than enhance the ability of private firms to develop new drug therapies. In particular, the more stringent regulatory climate for new pharmaceuticals that has evolved in the past two decades has been a major factor driving up the cost and development times for new drugs and in lowering R and D productivity in this industry. Longer development and regulatory approval times have also resulted in shorter real terms of patent exclusivity on new pharmaceuticals. Furthermore, at both the Federal and State levels, government officials have been enacting various programs designed to promote the use of generic drugs after patents expire and imitative drugs come on the market.

The resulting adverse economic trends from these public policies lend considerable doubt as to whether all the promising opportunities now available in pharmaceuticals will be exploited as rapidly as good science permits.

The drug discovery and development process now involves a long and costly set of investments and is subject to high levels of risk and uncertainty. Over the past two decades, R and D costs per new drug introduction have accelerated much faster than the rate of inflation or new drug revenues. Economic analysis indicates that the present value of R and D costs for producing a new drug introduction is now over 70 million dollars in current dollars (more than a tenfold increase since the early sixties) (Hansen, 1979). The process generally takes over 10 years from initial synthesis to actual commercial introduction (Wardell, 1979). Furthermore, my own research shows there are now substantially fewer independent industrial sources of pharmaceutical innovation than during the early post World War II period. Smaller U. S. firms in particular have dropped out of the business of discovering and developing new drugs (Grabowski and Vernon, 1976; 1977).

In this paper, an evaluation of the effects of regulatory and other policy measures on the drug innovation process is presented. A number of policy changes for improving the current situation are also considered.

The Importance of Drug Innovation to Medical Progress

The private pharmaceutical industry (that is, both domestic and foreign firms) has discovered and developed approximately 90 percent of the new drug entities introduced into the United States since 1950. It has also discovered a similar percentage of the new drug introductions classified as significant therapeutic advances by the Food and Drug Administration (Schwartzman, 1976). Industrial drug discoveries, of course, often build directly upon the knowledge generated by a large biomedical basic research effort undertaken at universities and public institutions such as the National Institutes of Health (Chain, 1963).

The revolutionary effects that new drug discoveries have had on the practice of medicine within the present century have been chronicled by a number of writers. Victor Fuchs (1974) has observed in this regard:

Until this century the physician could with confidence give a smallpox vaccination, administer quinine for malaria, prescribe opium and morphine for the relief of pain, and not much more. A quarter-century later the situation was not much different. Some advances had been made in surgery, but the death rates from tuberculosis, influenza and pneumonia, and other infectious diseases were still extremely high. With the introduction and wide use of

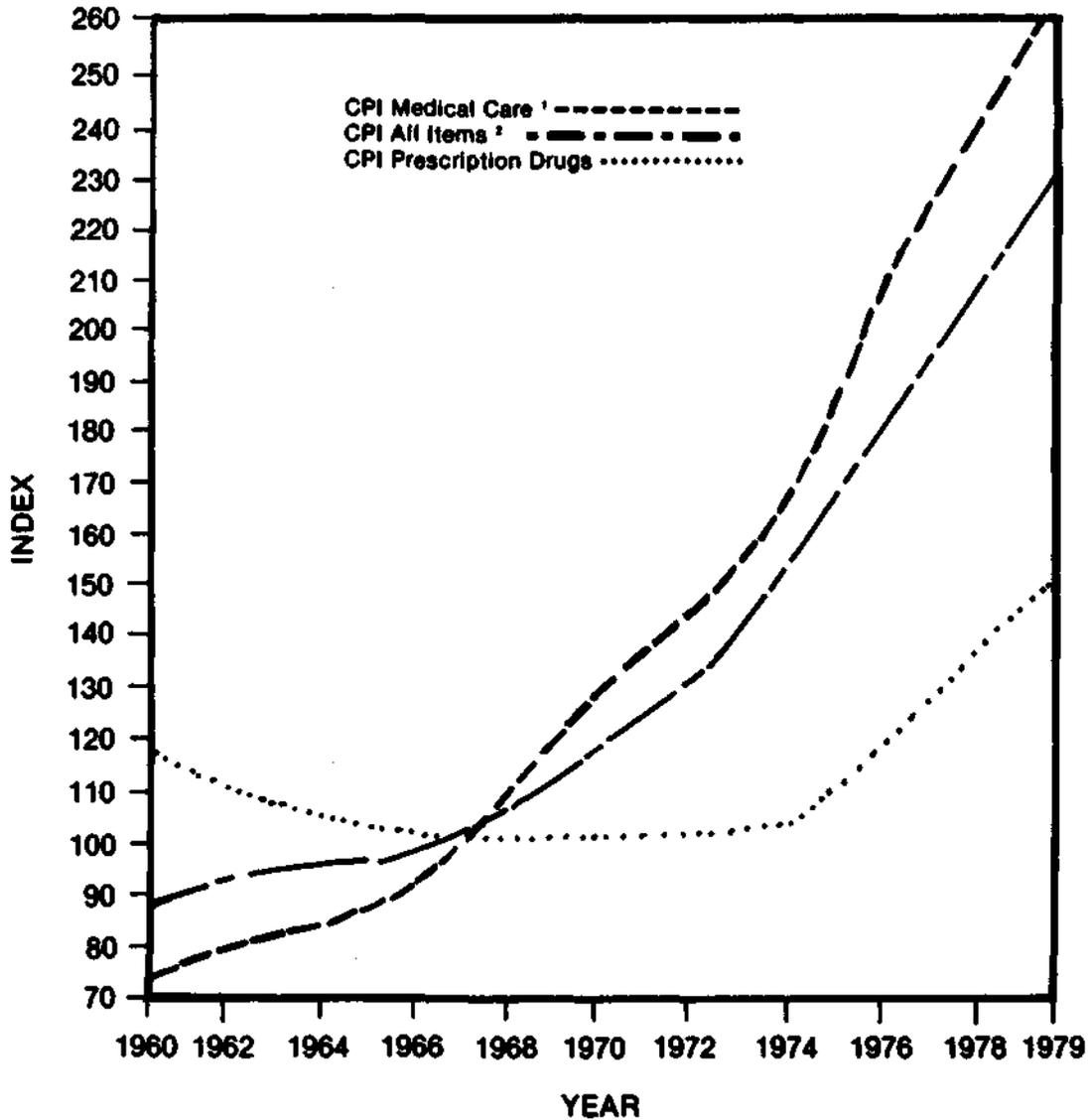
sulfonamide and penicillin, however, the death rate in the United States from influenza and pneumonia fell by more than 8 percent annually from 1935 to 1950. (The annual rate of decline from 1900 to 1935 had been only 2 percent.) In the case of tuberculosis, while some progress had been made since the turn of the century, the rate of decline in the death rate accelerated appreciably after the adoption of penicillin, streptomycin, and PAS (paraaminosalicylic acid) in the late 1940's and of isoniazid in the early 1950's. New drugs and vaccines developed since the 1920's have also been strikingly effective against typhoid, whooping cough, poliomyelitis, measles, diphtheria, and tetanus; more recently great advances have been made in hormonal drugs, antihypertension drugs, antihistamines, anticoagulants, antipsychotic drugs, and antidepressants.

As Fuchs observes, the decline in death rates from several major infectious diseases following the introduction of specific antibiotics and vaccines has been particularly striking.

The introduction of new drugs often yields significant benefits, as well, in the form of a reduced need for hospitalization and reduced levels of morbidity. This is demonstrated quite dramatically in the case of mental illness. Beginning in the 1950's the pharmaceutical industry introduced a number of therapies that were useful in the treatment of mental illness—tranquillizers, anti-anxiety and antidepressant drugs. These have had a strong positive impact on the amount of hospitalization for mental illness. The population in mental hospitals began to decline for the first time in 1956, two years after the introduction of the first of the major tranquillizers, Chlorpromazine. The number of patients declined from 565,000 individuals in 1956 to under 200,000 currently. As Doctors Earl Pollack and Carl Taube (1973) of the National Institute of Mental Health have stated, "there is no question that this decline has been due to the widespread introduction of psychoactive drugs into mental hospitals."

In recent years in the United States, there has been intensified policy concern with the rapid increase in medical care costs and the increasing share of total national resources going to this sector. Figure 1 shows a time plot of the medical care component of the CPI (excluding drug costs) since 1960. It has been growing at a significantly greater rate than the CPI for the overall economy. In contrast, the CPI for prescription drugs has advanced by less than half that for the economy as a whole (this is unadjusted for quality changes in pharmaceuticals which have been substantial over this period). As one might infer from this

FIGURE 1
Comparison of Consumer Price Indices
1960-1979 (1967 = 100)



¹Excludes drug component

²CPI(W)—Consumer Price Index for urban wage earners and clerical workers

Source: U.S. Bureau of Labor Statistics, *Consumer Price Index Detailed Reports*, various issues.

figure, pharmaceutical costs have accounted for a steadily declining share of the rapidly growing national expenditures on medical costs.¹ Furthermore, where a new pharmaceutical entity replaces other forms of medical treatment, there are often opportunities for dramatic resource savings. A recent study by Weisbrod and Geweke (1981), for example, suggests that the availability of the anti-ulcer drug, Tagamet, introduced in 1977 has led to significant savings over time in patient expenses because of the reduced need for surgical treatment of peptic ulcers and for related hospitalization. There are also many historical examples where pharmaceuticals have replaced more costly modes of treatment (for example in the cases of tuberculosis and polio) which show significant gains both therapeutically and in resource savings.

The overall health care delivery system is characterized by expensive professional manpower, labor intensive activities, and complex and expensive technical equipment—all factors contributing to its high rate of inflation. There has also been a proliferation of costly medical technologies in recent years such as open heart surgery, coronary bypass, and the expanded use of intensive care units. Yet the existing mode of treatment remains less than satisfactory in many areas. The three leading causes of death in the United States at the present time are heart disease, cancer, and stroke. A recent study by Hartunian, Smart and Thompson (1980) calculated the annual direct and indirect costs in 1975 of cancer at 23.1 billion dollars, heart disease at 13.7 billion dollars, and stroke at 6.5 billion dollars.² These high dollar values demonstrate the very great amount of patient benefits and national resource savings that are potentially realizable from better therapies or preventive measures for these major diseases.

As observed above, one of the main sources of optimism concerning current prospects for significant new drug therapies stems from important advances that have been made recently in basic biomedical research. There is an increasingly better understanding of the underlying courses of diseases and also of how drug compounds interact with basic physiological processes. According to Dr. William I. H. Shedden, vice-president in charge of clinical evaluation at Eli Lilly, scientists at Lilly and other firms

are now taking a "very fundamental biological approach" in much of their research. There is less random screening of drug candidates and more design of molecules to achieve particular targeted biological effects (Business Week, 1979).

There have been some striking successes emerging from this more basic biological approach. Sir James Black developed the beta-blocker family of drugs and the anti-ulcer drug Tagamet by using this type of approach. In particular, in each case, he synthesized molecules that would block the receptors on the surface of the body cells so as to prevent natural hormones from locking onto them and triggering undesirable activity in the nucleus of the cell (Bylinsky, 1976). A similar discovery by design approach was also employed in the case of Squibb's anti-hypertensive compound, Capoten (Magnet, 1981).

There is currently a great deal of drug research centered around the body's immune response system and, in addition, in enzyme chemistry and prostaglandins. The potential therapeutic applications are numerous, including more effective therapies in the major disease areas of cardiovascular diseases, stroke, and cancer. Recent advances in the area of recombinant DNA or "gene splicing" also promise important application to future drug discovery and development. This new process has been used to induce bacteria to produce insulin and interferon and has existing possibilities in several other areas (Bezold, 1981, Ch: 6).

In sum, there appears to be a number of promising avenues at the present time for R and D in the pharmaceutical industry which would provide important potential consequences for improvements in human health. However, whether present regulatory conditions will permit rapid exploitation of these scientific opportunities remains questionable. As we discuss further, later, the number of drugs being tested in man has been declining in recent years despite a rapidly expanding basic research base and increased R and D resource commitments from the major firms. In particular, the very high costs and gestation times now associated with discovering, developing, and gaining approval for new drug entities have forced firms to be very selective in their R and D strategies and testing. As Dr. Cuatrecasas (1980) of Burroughs Wellcome has observed, "We see daily a tremendous number of leads and suggestions, but fewer and fewer of these can be pursued and be taken to study in man. . . . Today we must make very early and premature decisions."

¹In calendar year 1980, spending for all prescription drugs, over the counter drugs, and medical sundries dispensed through retail channels accounted for 7.8 percent of national health expenditures. This share has declined from over 12 percent in 1965 (Gibson and Waldo, 1981).

²The direct costs involve medical care outlays. The indirect costs involve work force losses associated with illness and premature death. The methodology employed by the authors involves a lower bound approach from the standpoint of economic theory in that no attempt is made to measure or include the disutility (that is, "pain and suffering") experienced by those having these diseases.

Regulatory Objectives and Philosophy

Few would question the fact that safety regulation in pharmaceuticals provides important benefits to society. A new drug compound can be the source of important therapeutic benefits or present serious unforeseen toxic side effects. In the early stages of development, attempts to determine a drug's benefits and risks are characterized by a high degree of uncertainty that can be reduced only by further tests on animals and humans. A regulatory agency can provide important societal benefits by insuring that the information gathered from clinical research is performed with minimal risks to research subjects and that new drug introduction decisions are based on a *balanced* assessment of benefits and risks to patients.

It is important to keep in mind, however, that excessively stringent or cautious regulation, because of its adverse effects on the innovation process can have undesirable effects on human health just as too little regulation can. The resulting benefits must necessarily diminish while R and D costs and development time correspondingly increase. With finite R and D resources, some drugs of a beneficial character will not be developed. In addition, consumers will have to wait longer to receive the benefits of drugs having superior therapeutic properties to those already in the marketplace. Thus human health can be adversely affected by too little or too much regulatory control.

There is considerable evidence accumulating from a variety of sources that regulation of drugs since the early sixties has become excessively stringent. What is the source of this regulatory unbalance? There have been many analyses of this question. Some basic factors are worth emphasizing before examining specific empirical studies.

First, the incentives present in the current regulatory process are very skewed in character. The legislative mandate and regulatory procedures evolved over time as a response to the perceived problems associated with unsafe and ineffective drugs. Little thought was given to the potential adverse effects on drug innovation. FDA personnel have been much more concerned with avoiding one type of error (acceptance of a "bad" drug) than with the commission of another type of error (rejection of a "good" drug). In particular, the regulatory official stands to bear heavy personal costs from the approval of a drug which is subsequently shown to be unsafe or ineffective. Such an outcome, even if it occurs very infrequently, tends to be highly visible and is one for which both the FDA and the regulatory official involved will be held politically accountable. At the same time, the costs of rejecting or delaying a good drug are borne largely by outside parties (drug manufacturers and sick patients that might benefit from its availability). They are also much less visible in nature.

As a consequence of this much greater incentive to err on the side of rejection, there is a strong tendency toward requiring excessive amounts of testing before granting approval and to very long delays in making regulatory decisions. Consequently many useful drugs are delayed or are not introduced at all because of the adverse effects of this regulatory philosophy on the innovation process.

In the years since the early sixties when the Thalidomide tragedy occurred and the 1962 Amendments were passed, the signals emanating from Congress and the media also have tended to reinforce the natural incentives toward risk-averse behavior by FDA officials. Former FDA Commissioner Schmidt (1974) has emphasized the problems these external pressures create for the maintenance of a balanced and rational decision-making structure. He has observed in this regard,

"The message of FDA staff could not be clearer. Whenever a controversy over a new drug is resolved by its approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made. The Congressional pressure for our negative action on new drug applications is, therefore, intense. And it seems to be increasing, as everyone is becoming a self-acclaimed expert on carcinogenesis and drug testing."

Drug Lag

The most frequently researched and documented outcome of these skewed incentives is the slowness by which new drug introduction decisions are made and the corresponding "drug lag" which has occurred vis a vis other developed countries. Professor William Wardell (1973) was the first individual to do a systematic comparison of new drug introductions in the United States and the United Kingdom for the decade following the 1962 Amendments. He found that in this period there were 50 percent more new chemical entities (NCEs) introduced into the U.K. and in addition, for the class of mutually available drugs, more than twice as many were introduced first in the U.K. Since his initial study, there have been numerous follow-up studies by Professor Wardell and others, including one recently by the U. S. General Accounting Office (1980) which reached similar conclusions.

A basic objection that FDA officials have consistently raised to the analysis of drug lag has been the use of NCE introductions as the basic measure of technological advance. In particular, they have argued that what is important is not the total number of new pharmaceuticals available but the *quality* of the NCEs that do become available. However, the question of drug quality has been addressed in several of these studies including the recent analysis of the U. S. General Accounting Office. In particular the GAO study examined the introduction pattern in several countries of all drugs classified by the FDA as important

therapeutic advances for the period July 1975 through February 1978. Of these 14 important drugs, all but one were available earlier in at least one foreign country before they were available in the United States. They also found, for example, that disopyramide, used to treat abnormal heart rhythm, was available more than 5 years earlier in the United Kingdom; the beta blocker propranolol, an important advance in treating high blood pressure at the time of its introduction, was available more than 7 years earlier for this use in the United Kingdom; and, sodium valproate, used to treat epilepsy, was available about 6 years earlier in Switzerland.

Another related finding of the GAO report was that the 14 important drugs had approval times that were considerably shorter abroad compared with the approval times in the United States (with Sweden being the main exception).

Of course, not all of the observed drug lag is due to FDA actions and the U. S. receives some benefits from its slower, more cautious regulatory process. The House Subcommittee on Science Research and Technology Report (1980) on the FDA's process for approving new drugs listed five drugs introduced abroad that were later withdrawn because of toxicity problems.³ The U. S. was thus spared some toxicity associated with these particular drugs by its slow moving, more conservative regulatory posture.

Nevertheless, the evidence appears to indicate that these benefits were small relative to the foregone benefits of having some of the major advances in cardiovasculars and other areas available sooner for treatment of patients. As noted earlier, the beta blocker propranolol was approved for use in the treatment of hypertension in the United States seven years after the United Kingdom approved it. Furthermore, no beta blockers were approved for use in treating patients who survived heart attacks until Timolol was approved in November 1980. Professor Wardell calculated that the effect of not having any of the beta blockers sooner to treat heart attack patients, despite earlier evidence from European data that at least two of them significantly reduced mortality from second heart attacks, was the loss of several thousand lives a year (U. S. House Subcommittee Hearings, 1979; p. 797-798).

Drug Loss

While maximum attention in the literature has centered around the drug lag phenomenon and the new drug application (NDA) approval phase of the regulatory process, this is only one part of a complex set of

³The Summary Report of the House Subcommittee (1980) notes that the most significant of these recalled drugs appears to be Practolol. This beta blocker drug leads to severe conjunctivitis resulting in impaired vision for a small number of patients to which it was administered. However, a number of medical experts also testified that Practolol had a high benefit to risk ratio for certain treatments and that its toxicity could be managed under proper medical procedures.

regulatory constraints on the innovative process. Dr. Richard Crout (1978), director of the Bureau of Drugs of the FDA has pointed to two other aspects of the 1962 Amendments with particularly significant impacts on innovation over the past two decades—(a) the requirement for adequate and well controlled trials in demonstrating efficacy as well as safety; (b) the requirement that clinical research on drugs be regulated under the investigational new drug (IND) process. He has observed in this respect, "It is no secret that these gains have been purchased at the cost of increased time and money for new drug development."

Figure 2 shows a time plot of pharmaceutical R and D expenditures versus the introduction of new chemical entities for the period 1954 to 1979.⁴ As one can see from this graph, there has been a secular decline over time in total NCE introductions while total industry R and D expenditure has been steadily increasing in real terms. This implies there has been a significant decline in "R and D productivity" or the real resources necessary to discover and develop a new drug entity. In fact, R and D productivity has declined by more than tenfold over the decades of the sixties and seventies.

Increased regulation has not been the sole factor responsible for this declining productivity in the pharmaceutical innovational process. Other hypothesized factors discussed in the literature include changing scientific fields of opportunity, increasingly stringent liability laws, and the more sophisticated and costly scientific methodology for detecting toxicology problems. Nevertheless, a number of studies point to regulation as a primary factor underlining this adverse trend.⁵

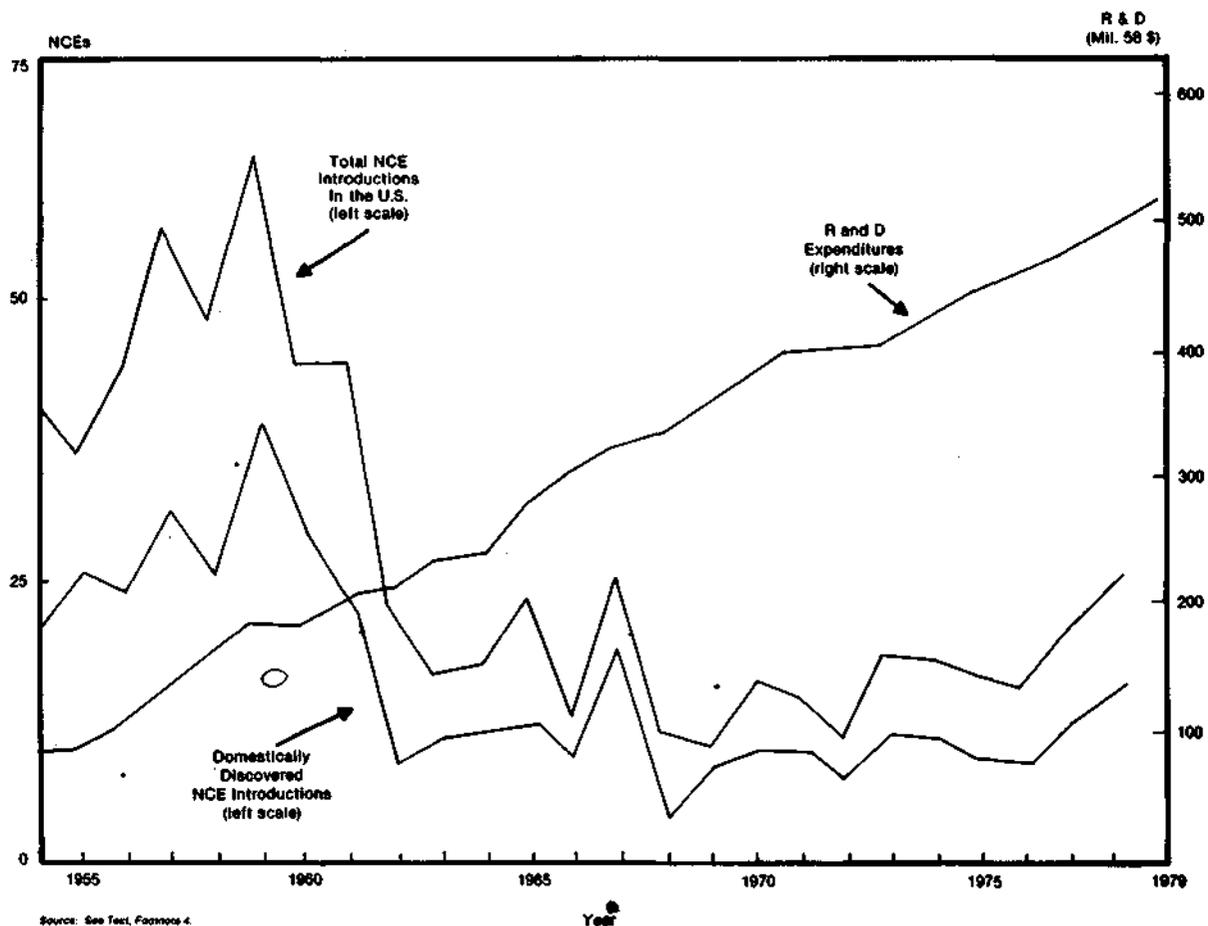
In a comparative analysis of the R and D cost per NCE discovered and developed in the United States and United Kingdom over the period 1960-61 to 1970, John Vernon, Lacy Thomas, and I (1978) found R and D costs have risen significantly in both countries. However, the rate of increases in cost per NCE was relatively much faster for the United States. On the basis of a statistical analysis drawing on the experience in the two countries, we concluded that U. S. regulation had been a major factor causing the more rapid increase in the United States. There was

⁴Date on new chemical entity introductions were obtained from the publications of Paul de Haen. Biologicals and diagnostics were deleted due to the problems of data availability and reliability prior to 1966. Research and development expenditure data were obtained from the annual surveys of the Pharmaceutical Manufacturers Association. These R and D data were deflated to constant (1958) dollars using the implicit price deflator for the Gross National Product. Detailed analyses of these procedures and sources can be found in the appendix to Grabowski, Vernon and Thomas (1978), p. 160-161.

⁵A review of this literature prior to 1976 is contained in Grabowski (1976) Chapters 2 through 4. This study has recently been updated and will be published in 1982 as a monograph, jointly authored with John M. Vernon, by the American Enterprise Institute.

FIGURE 2

Introductions and Discoveries of New Chemical Entities and Constant Dollar Expenditures on Pharmaceutical Research and Development in the United States



also a strong relationship over time between declining R and D productivity in the U. S. and a proxy measure of overall FDA regulatory stringency based on new drug approval times.

The rapid increase in R and D costs and development times and the corresponding decline in R and D productivity suggests there is likely to be a "drug loss" as well as a drug lag resulting from excessively stringent regulation. Of course, it is impossible ever to provide any precise accounting of the drugs *not discovered or developed* because of increased regulation. That such a drug loss phenomenon probably exists on a significant scale, however, is strongly suggested by some recent data developed by Professor Wardell (1979) on the IND filings of U. S. firms over recent years. His studies show that the annual rate of IND filing for U. S. owned NCEs generally declined from 1965 to 1972, whereas the rate was fairly constant for foreign owned NCEs over the entire period from 1965 to mid 1975. Since 1972, the average number of NCEs taken into human investigations by U. S. firms declined sharply (by 40 to 45 percent) during 1975-1976. Wardell's studies also show that U. S. firms are getting an increasing number of NCEs on license from foreign firms.

Economic Costs and Returns

My colleague, John Vernon, and I recently performed a sensitivity analysis on the profitability of the 37 U.S. discovered new drug introductions during the period 1970-76 (Grabowski and Vernon, 1982). For each of these 37 new drug introductions, we calculated a profitability index which is defined as the ratio of the present value of projected revenues to the present value of R and D costs. Current and historical data on costs and revenues were used to extrapolate values to future periods using a number of alternative assumptions.

A major finding of our analysis is that if the *real* interest rate is 10 percent, the product life must be 19 years for our sample of 37 drugs before the mean profitability index reaches one in value. Stated another way, it takes 19 years for firms to cover average R and D costs and earn a 10 percent real rate of return on their invested capital (that is, net of inflation). At an 8 percent real rate of return, product life must be 12 years in value.

These required payback periods can be usefully compared to the average effective patent lifetimes in this industry. As a result of the lengthening development and approval times, patent terms have been significantly declining. The average effective patent lifetime for all the new drug introductions for the period 1977 to 1979 was just under 10 years (Eisman and Wardell, 1981). Hence, a significant part of the nominal patent life of 17 years generally has expired before a new drug therapy can be put on the market.

Another major finding of our recent economic analysis is that the rate of return distribution for new drug therapies is highly skewed in character. A few drugs have very high rates of returns. However, we found that, even if one assumes a 20-year lifetime for all of the 37 new drug introductions in our sample, only 13, or roughly one third, had a profitability index of 1 or more in value. This indicates that the majority of the new drug introductions do not cover their full R and D investment costs (that is, when allowing for both discovery costs as well as the large attrition rate on new product candidates or "dry holes"). In effect, firms are dependent on a relatively few "big winners" to cover their full costs and generate the required return on their R and D investment portfolio.

These results, therefore, underscore the fact that the research intensive firms are increasingly dependent on a relatively small number of major new drugs, those capable of winning relatively large market shares, here and abroad, to finance and provide the returns on their overall portfolio of R and D investment projects. These major products, however, have had diminished patent life over time. They also provide the most attractive markets for generic follow-on producers. The degree of competition provided by these latter firms has been increasing in the new marketing environment characterized by drug substitution laws and government reimbursement programs. In particular, the Federal government has developed the Maximum Allowable Cost (MAC) program to reimburse Medicare patients only for the lowest cost product. Furthermore, most States have passed substitution or product selection laws, allowing (some mandate) pharmacists to dispense alternative products to the brand specified on the prescription form (unless doctors explicitly prohibit substitution on the form) (Grabowski and Vernon, 1979).

In effect, the cumulative economic effect of U.S. public policies over recent years has been to drive up the R and D costs and development times, shorten effective patent lives, and encourage generic product utilization in the period after patent expiration. Although all of these policy efforts have been well-intentioned and addressed to valid social goals, taken in combination, they have the effect of significantly adversely affecting the economic incentives and capabilities of many firms to invest in pharmaceutical research and development.

Policy Remedies—Patent Restoration

Legislative bills embodying the concept of patent restoration for industries subject to premarket approval have been introduced into both branches of Congress.⁹ In the case of ethical drugs, this proposed legislation would add back to the patent life, at the time of FDA approval, any time lost during clinical testing and NDA regulatory review, up to a maximum of seven years.

The concept of patent restoration has been advocated by a number of government policymakers and advisory groups. For example, Former President Carter's Domestic Policy Review on Industrial Innovation recommended patent life restoration for the full class of products now subject to premarket review (that is, ethical drugs, food additives, pesticides, and certain medical devices). In addition, the Secretary of HHS, Richard Schweiker, FDA Commissioner Hayes, and the authors of the Federal Trade Commission's Model Substitution Law have at different points in time all urged Congress to seriously consider this policy measure as a way of compensating for innovation disincentives arising from other public policies.

The patent restoration concept has a number of attractive elements. It provides a way of enhancing the economic incentives to those firms that are most successful in developing new drug introductions. As discussed above, average effective patent periods are now generally shorter than average payback periods for profitable operation. In the emerging environment of increased competition from generic products, the length of patent protection is likely to become an increasingly important factor underlying the willingness of firms to undertake costly and risky R and D activity.

Patent restoration, while providing significant positive incentives for new drug investment outlays, cannot fully compensate, however, for the time and resources used up in the regulatory process. This is because patent restoration influences only the latter years of product life. Many products will have competition from rival firm introductions before the period of patent restoration comes into play. Furthermore, the value in economic terms of time added on to the end of the patent period will be worth much less than the value of the time lost from increased regulatory compliance time at the front end of product life. This reflects the time value of money. In our sensitivity analysis, for example, we found that a 1½-year reduction in the time it takes for a new drug application to be approved would reduce the time it takes a drug company to recoup its R and D investment by a full 5 years—from 19 years to 14 years (Grabowski and Vernon, 1982).

⁹As of the time of this writing, S255, the Patent Term Restoration Act had passed the Senate in June 1981. A similar bill, HR 1937, was being considered in hearings in the House of Representatives.

Regulatory reform must, therefore, be a high priority matter even if patent restoration is enacted. An extensive number of academic and government studies have now analyzed and made recommendations for improving the drug regulatory process. Several recurrent themes for substantive policy change have been proposed in these studies. These are briefly considered here.

The Clinical Research Process

One important step for enhancing drug innovation would be greater flexibility in the early stages of clinical research. Because of the uncertain recursive nature of the research process, regulatory delays at this early stage can have a large compound effect on resource costs and time. Generally, about ten substances are tested clinically for every one that is taken through full development to a new drug application (NDA) with the FDA. However, the information garnered from testing the unsuccessful compounds on a small number of individuals in Phase I and II provides a cumulative feedback effect that is incorporated into successful drug therapies. Delays in the early stages of clinical process therefore have a compound effect on outcomes and tie up the most creative part of a firm's research organization.

Clinical trials are currently approved and supervised by institutional review boards at the medical centers where they are performed in addition to the controls exercised by the FDA in the IND process. The safety record in these early trials is very good. This is because of the intensive monitoring and highly controlled nature of early clinical trials. Doctors Phillippe Cardon, William Dommel and Robert Tumble (1976) of the National Institute of Health have reviewed the injury data to research subjects and concluded in this regard "the data suggest that risks of participation in nontherapeutic research may be no greater than those of everyday life and in therapeutic research, no greater than those of treatment in any other setting."

Decentralizing primary responsibility for early clinical trials into the hands of institutional review boards is a recommendation of several recent studies of the drug process including the GAO (1980) and the House Subcommittee on Science Research and Technology (1980). Under one frequently recommended institutional arrangement, the FDA would issue general regulations and then certify certain delegated health institutions (such as research hospitals) to approve and supervise Phase One and Two clinical investigations. The FDA would still retain oversight authority, however, to revoke any drug investigations approved by these delegated institutions.

Pre versus Post Marketing Controls

More reasonable pre-marketing standards combined with increased post-marketing surveillance is another step that can be taken to foster the innovative process. In the current system, drug regulation has an all or nothing approach. Before approval, candidate drugs are restricted to small patient populations under highly controlled experimental conditions, while after approval, usage often increases with minimal regulatory surveillance. Given these circumstances, it is not surprising that regulatory officials tend to err on the side of conservatism in new drug approvals.

The FDA pre-marketing approval conservatism has manifested itself by an evolving expansion over time in its interpretation of what constitutes "adequate and well controlled" investigations of a drug's safety and effectiveness. This frequently puts investigators at the FDA in the position of delaying a drug's entry into the market until the "pivotal" scientific studies are performed, even where there is little doubt about a drug's safety or effectiveness. At the same time, low incidence risks (those occurring less than one per thousand) generally cannot be detected in clinical studies of a few hundred patients. The best way to detect these is through more extensive and effective post-marketing monitoring.

Many observers have argued that post-marketing controls could effectively replace some of the large scale Phase III clinical trials now required by the FDA. This appears to be an attractive concept that warrants serious attention by policymakers. Properly implemented this could lead to both lower R and D costs and speedier introduction of new drugs.

Research Data From Abroad

The problem of "drug lag" could be reduced in some cases if the FDA were to place greater reliance on foreign clinical data. Prior to 1975, the FDA accepted no foreign data as positive evidence in support of NDA approval. Since then foreign data have become acceptable provided they meet FDA's criteria in terms of the quality of scientific research. Nevertheless, the usual requirement is that at least two U. S. studies be conducted to supplement and verify this evidence.

Drug discoveries from foreign laboratories now account for approximately 40 percent of U.S. introductions, and U.S. firms presently are conducting an increasing percentage of their research and development abroad (Grabowski, 1976; Wardell, 1978). Certainly a mechanism is needed within the FDA to evaluate foreign clinical data and determine, on a drug-by-drug basis, whether or not it meets the intent of U.S. criteria and can be used in lieu of any domestic trials. This would be consistent with FDA's stated policy to consider all clinical studies on their merits regardless of country of origin.

Regulatory Procedures and Incentives

Inadequate management and operating procedures at the FDA have been a frequently cited cause of unnecessarily long NDA approval times (at present approximately two years as compared to six months in the United Kingdom). The recent GAO report (1980), for example, provides a detailed investigation of the factors that contribute to slow approval times. These factors include imprecise FDA guidelines that are subject to varying interpretations, inadequate mechanisms for resolving scientific disagreements between FDA and industry, slow or inadequate FDA feedback to industry on deficiencies, limited reviewing time, and uneven workloads.

While a number of studies have focused directly on FDA management deficiencies, it should be borne in mind that the underlying problem here is not simply one of good or bad management techniques, but rather more fundamentally one of organizational incentives. As noted earlier, FDA incentives are strongly skewed toward officials avoiding the acceptance of a "bad" drug while being much less concerned about rejection or delay of a "good" drug. The agency's mandate evolved as a response to a few widely publicized drug tragedies and is drawn in very narrow terms, that is, to insure the safety and efficacy of new drug products. All of the burden of proof rests on the sponsoring firm to demonstrate this to the satisfaction of the regulatory authorities. In view of these characteristics it is not surprising that the drug approval process is a long and costly affair or that the GAO and others have found management deficiencies in the agency.

Assuming that we want to retain the basic framework of pre-market approval of new drugs, and there appears widespread support for this at the present time, the most important changes for a speedier and more efficient regulatory process involve changes in the current structure of regulatory incentives. This is not an easy task to accomplish through either legislative or administrative policy measures. There are some approaches that appear worth pursuing however.

First, it is important for members of Congress in oversight and other hearings to send FDA clear signals that it wants "approvable" drugs handled in a more efficient manner and available to the public as expeditiously as possible. There appears to be an increasing recognition of the drug lag problem within Congress and some progress along these lines has already begun to occur as attested to by the appointment of a Congressional Commission on the Federal Drug Approval Process in 1981.⁷

One aspect of the current law that Congress could underscore at this time is the requirement in the 1962 Amendments that FDA approve or disapprove a drug within 180 days. This is honored in the breach. The average time necessary to review and approve a new drug application is about two years. At the same time, over 90 percent of all new drug applications are eventually approved by the FDA, although some take five years or more (Wardell, 1979).

At the current time, Congress could fruitfully reaffirm the original intention in the 1962 law that drugs be approved within a reasonable time frame. To reinforce this policy objective, it could set up a review process involving outside experts that could be triggered when a drug fails to have an FDA approval or rejection decision within such a reasonable period. The intention here would not be to impose a rigid straightjacket on the regulatory review process, but rather to create the expectation that an approvable drug will receive a reasonably speedy, efficient regulatory decision, and exceptions (which may be perfectly valid) would be subject to outside review by medical experts and advisory committees. Furthermore, to the extent that inadequate financial resources are an obstacle to creating such an efficient process, serious consideration should be given to charging firms a licensing fee to cover part of the FDA costs.

The GAO and House Subcommittee Report on Science, Research and Technology have also advocated a stronger role in decision-making by expert advisory committees to the FDA. They note this is a positive aspect of several foreign country regulatory systems. Such committees are likely to balance benefits and risks in a more representative fashion than career civil servants, and their recommendations serve as an important buffer between the agency and various political groups and advocates. Outside medical experts might also be utilized to deal with scientific disputes in a more effective manner than legal suits in

the judicial system. Our regulatory system has become unnecessarily adversarial in character compared to European countries such as the United Kingdom where such appeals mechanisms exist to settle scientific disputes.

It is important that the scientific advisory panels have the final say in scientific decisions and judgments, as is the case in several European countries, if this is to be a positive reform measure. At the current time, FDA has outside advisory committees for each major therapeutic area. Nevertheless, it appears these committees are often used in an "after the fact" manner to ratify decisions already made by the FDA officials. In addition, participation on these committees has been severely restricted by the Justice Department's interpretation of conflict of interest laws. Specifically, the current interpretation of these laws is that even a scientist with no ties to a FDA-regulated firm but who is affiliated with a university that receives research support from a pharmaceutical firm (for example, under an IND study), cannot serve on such a committee without a special exemption. This restrictive interpretation frequently disqualifies most of the individuals with the greatest expertise and experience.

Hence, while use of outside advisory committees has been frequently recommended as a means of encouraging a more balanced regulatory process and to augment existing internal scientific expertise and resources, the potential in this regard to date has been largely unrealized in this country. In many cases they have actually served as an additional regulatory layer that must be hurdled for a new drug approval. In a few notable cases, for example, sodium valporate, the advisory committees have played an important role in getting the FDA to speed new therapies into the marketplace. This appears to be the exception rather than the rule.

While Congress can provide the broad directions and necessary resources, substantive reforms in a case-by-case regulatory review system are ultimately accomplished on a day-to-day basis in terms of specific regulatory decisions and procedures. Hence it is critically important that the current FDA administrative leadership take decisive action to implement needed changes in regulatory procedures.

⁷In the summer of 1981, a twenty-five member Congressional Commission on the Federal Drug Approval Process was established under the sponsorship of Representatives Scheuer and Gore. This committee of experts from the scientific, public, industry, and government sectors is chaired by Dr. Gilbert McMahon of Tulane University. It has been asked to develop recommendations on how FDA's procedures for the approval of new drugs can be expedited. Their final report was pending at the time this paper was written. It should address all phases of the new drug approval process and provide inputs into the proposed regulatory changes now under review by the Administration.

Conclusions

The activist government policies of the past few decades have been a major factor contributing to the adverse trends observed in the case of pharmaceutical innovation. Public policy in pharmaceuticals has been characterized by increasingly stringent regulatory controls, shorter effective patent terms, and increasing encouragement of generic product usage. While all of these policies have been well-intended, in combination, they have produced significant unintended adverse side effects on the drug innovational process. They have contributed to the present situation of fewer independent domestic sources of innovation and fewer annual new drug entity introductions. This has occurred despite a steadily expanding base of rich, scientific, opportunities emerging from basic research endeavors.

Outside the support of basic research, there has been very little attention given by policymakers to the effects of government policy on industrial innovation. This is a particularly myopic and sub-optimal approach to public policy. Historically, new drug innovations have played a central role in medical progress. Furthermore, new drugs have frequently replaced much more costly and less effective medical treatments, leading to substantial resource saving in medical expenditures. Hence, economic and health gains generally have been realized in a complementary fashion.

It is now time to reform our regulatory and other industrial policies to insure that a conducive atmosphere for vigorous competition in new drug innovation will hold in the years ahead.

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